NEW YORK HEART ASSOCIATION

ABSTRACTS OF PAPERS PRESENTED AT THE SCIENTIFIC SESSION ON RESEARCH

HELD AT HEART HOUSE, NEW YORK, N.Y.
APRIL 25, 1978

*Biosynthetic Processes Related to the Stimulation by Insulin of Sodium Transport in the Toad Bladder**

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PORCINE insulin (20 mU/ml.) increases sodium transport in toad urinary bladder, an effect evident after 30 minutes that persists for at least 20 hours. The initial phase (up to 90 min.) of the increase in sodium transport is not blocked by inhibitors of protein or RNA synthesis, i.e., puromycin and actinomycin D, respectively. These inhibitors did, however, inhibit the sustained (90 min.-20 hr.) insulin-induced increase in short circuit current (SCC). Although there is an initial increase after 60 minutes, the SCC is indistinguishable from control values. To verify that insulin stimulates the synthesis of macromolecules, we first examined the effects of insulin on the labeling of mRNA in the mitochondria-rich (MR) and granular (G) mucosal cell populations. In both MR and G cells we found a rapid (45 min.) increase in incorporation of ^{3}H-uridine into mRNA, which is linear up to three hours. In addition, we found a large increment in the synthesis or accumulation of tRNA and rRNA. We were able to measure a 52% increase in uridine incorporation and a 67% increase in leucine incorporation into polyribosomes from cells treated with insulin (500

*This paper was selected by the Committee on the Scientific Session on Research of the New York Heart Association to receive the associations ninth annual J. Murray Steele Award, established in honor of the late J. Murray Steele, M.D., a director of the New York Heart Association, 1951-1964, for the best presentation before the Scientific Session on Research.

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mU/ml.) for 120 minutes. Using a double label technique, we next studied the effect of insulin on the incorporation of amino acids into cytoplasmic and plasma membrane proteins. After 60 minutes we found at least one insulin-induced protein in the G cell cytoplasm, but none in the plasma membrane. After longer incubations (180 min.), the induced protein(s) present at 60 minutes were no longer found in the cytoplasm, but there was increased labeling of one membrane protein with the same molecular weight (20,000 daltons) as the cytoplasmic protein observed at 60 minutes. This suggests that the induced protein moves from the cytoplasm into plasma membrane within three hours. We labeled insulin-treated bladders with ^{125}I using lactoperoxidase and found increased labeling of a G cell plasma membrane protein of 20,000 daltons. We are currently investigating the relation between insulin-induced proteins and the changes in sodium transport. *(Supported by The American Heart Association and the National Institutes of Health.)*

Ion Entry into Gramicidin A Channels is Diffusion-Limited

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We studied current-voltage characteristics of Gramicidin A (Gram A) single channels in di-phytanoyl-PC bilayers at low aqueous concentrations of Na^+, K^+, Rb^+, Cs^+, NH_4^+, Ag^+, and Tl^+. At high potentials (0.3 to 0.5 V) the current reached a limiting value independent of the applied potential (slope conductance ≈zero). The magnitude of the limiting current (1.5 to 7 pA in 0.1 M salt) was consistent with the notion that ion entry into Gram A channels is limited by diffusion in the aqueous phases. The limiting currents for the alkali metal ions and NH_4^+ can be scaled by their aqueous diffusion coefficients, and the limiting current decreases with the diffusion coefficient when the viscosity of the aqueous phases is increased by addition of sucrose. The conductance-voltage characteristics observed with these ions is monotonic declining, indicating that ions moving through the channel cannot be in distribution equilibrium with the aqueous phases. The limiting currents observed with Ag^+ and Tl^+ were two to three times larger than predicted from the aqueous diffusion coefficients and the currents observed with the alkali metal ions and NH_4^+. This indicates that the effective area of the channel is much larger for Ag^+ and Tl^+ compared with the other ions. This increased area probably can not be ascribed to an increase in the luminal diameter of the Gram A channel, as the permeability coefficient to urea is unaffected by the presence of Ag^+ or Tl^+. These ions can, however, induce small changes in the channel structure, as the single channel life time is about five times longer in the presence of Ag^+ and Tl^+ (1.1 to 1.4 seconds) compared to the alkali metal ions and NH_4^+ (0.16 to 0.25 seconds). (*Supported in part by Grant GM 21342 from the National Institute of General Medical Sciences, Bethesda, Md.*)

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Effect of Ischemic Arrest on Regional Force-Length Relations of the Canine Left Ventricle

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ALTHOUGH reduced compliance of the arrested left ventricle (LV) may reflect irreversible myocardial injury, a simple method to detect early changes in compliance during ischemia has not been reported.

We used a pressurized cylinder to monitor regional compliance during the onset of rigor in the isolated canine left ventricle. The cylinder was activated through a fluid coupling, permitting the gauge to be sterilized. The pressure within the gauge and the length of a segment of myocardium included between stainless steel pins were correlated to produce force-length (F-L) curves for the left ventricular free wall.

In six excised, arrested left ventricles, serial pressure-volume (P-V) curves were recorded over a three-hour period until rigor developed. Mitral and aortic valves were sealed with clamps, and fluid was introduced in 5 ml. increments while pressure variations were recorded with a Statham transducer. F-L curves were simultaneously obtained using the gauge on the anterior left ventricular wall. With the onset of rigor, P-V and F-L curves manifested parallel shifts upward and to the left so that small incremental increases in volume or muscle length produced marked elevations in filling pressure and left ventricular wall force.

We conclude that regional force-length curves of the left ventricular myocardium can be used to monitor changes in global left ventricular compliance. This technique may allow changes in the compliance of the arrested left ventricle to be detected before the onset of irreversible ischemic injury. (*Supported in part by Grant HL12758-10 from the National Heart and Lung Institute, Bethesda, Md.*)

Hemodynamics of Dopamine and Isoproterenol in Acute Canine Beta Adrenergic Blockade

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ALTHOUGH propranolol has been recommended by some clinicians for intraoperative myocardial protection and denigrated by others because of its myocardial depressant effects, the proper pharmacologic methods for circulatory support should heart failure occur in the presence of propranolol (PROP) are not well understood. Accordingly, hemodynamic effects of dopamine (DOPA) and isoproterenol (ISO) were examined in randomized fashion before and after PROP, 1 mg./kg., in six anesthetized, open-chest mongrel dogs. The stimulating effect of a "test" dose of ISO (0.06 mcg./kg./min.) on cardiac output (CO) was closely reproduced after PROP by 1.2 mcg./kg./min. ISO, 20 times the test dose (CO 2.92 ± 0.28 and 2.93 ± 0.21 L/min., respectively). After PROP, ISO increased heart rate (114 ± 5 versus 145 ± 7, $p < 0.05$), decreased systemic resistance (38 ± 2 versus 24 ± 1 $p < 0.01$), and slightly increased peak LV dP/dt, recorded by micromanometer (1,278 ± 185 versus 1,929 ± 62 $p < 0.06$), compared to PROP alone.

Following PROP, DOPA (50 mcg./kg./min.) failed to achieve CO levels attained with a test dose (10 mcg./kg./min.) before PROP 3.3 ± 2 versus 2.0 ± 2 L/min. $p < 0.05$) and substantially raised mean aortic pressure (120 ± 17 versus 150 ± 18 mm. Hg $p < 0.05$) and peripheral resistance (37 ± 5 versus 80 ± 15 $p < 0.05$), compared to "test."

Additional measurements of pressures in right atrium, right ventricle, pulmonary artery, left atrium, left ventricle, and aorta confirm the impression that large doses of ISO following PROP increase cardiac output primarily through peripheral beta effects, while DOPA acts primarily as an alpha agonist.

These results suggest that optimum hemodynamic results in the low output syndrome in the presence of propranolol would be achieved by administration of a combination of high dose isoproterenol (10 to 20 times standard) and standard doses of dopamine. (*Supported in part by Grant HL12738-10 from the National Heart and Lung Institute, Bethesda, Md.*)

Hemodynamics of Dopamine and Isoproterenol in Chronic Canine Beta Adrenergic Blockade

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APPROPRIATE pharmacologic treatment of low output syndrome in the presence of propranolol (PROP) is not well defined, despite increasingly widespread use of PROP in surgical patients. Previous studies in our laboratory have shown that during acute beta adrenergic blockade in dogs, isoproterenol (ISO) can increase cardiac output in 10 to 20 times normal doses, primarily through actions as a peripheral vasodilator and secondarily through its inotropic and chronotropic actions on the heart. In the same setting, dopamine (DOPA) acts primarily as an alpha-agonist, causing peripheral vasoconstriction. In the present study, more closely simulating clinical situations, ISO and DOPA were tested in chronic beta adrenergic blockage. In eight dogs PROP was administered orally and a minimal heart rate response to ISO, 0.03 mcg./kg./min. was used to confirm beta blockade. To achieve this, 240 to 320 mg. PROP per day was required over a two-week period.

Animals anesthetized with pentobarbital and chloralose were studied after thoracotomy and cannulation of right ventricle, pulmonary artery, left atrium, and aorta for pressure recordings. LV pressure was measured by micromanometer and cardiac output (CO) by thermal dilution. In this setting DOPA was a more powerful beta agonist than in acute PROP blockade, but additional beta support was needed. Optimum hemodynamics were achieved in five animals by combined administration of DOPA 10 mcg./kg./min. and ISO 0.4 mcg./kg./min. Compared to controls, this combination increased systolic arterial pressure (110 $\pm$ 25 (S.E.) versus 138 $\pm$ 25 mm. Hg), CO (2.6 $\pm$ 0.4 versus 4.0 $\pm$ 7 L/min.), and heart rate (113 $\pm$ 10 versus 159 $\pm$ 10), $p < 0.05$. These results provide a model for the combined use of DOPA and ISO in the therapy of the low output syndrome in chronic beta adrenergic blockade. (*Supported in part by US PHS Grant HL12738-10 from the National Heart and Lung Institute, Bethesda, Md.*).

Factors Conditioning the Positive Inotropic Action of Strophanthidin in Cardiac Purkinje Fibers

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WE perfused canine Purkinje fibers *in vitro* and studied the effects of strophanthidin on the electrical and mechanical events in the presence and absence of tetrodotoxin. Tetrodotoxin) (~ 10^{-5}M) reduced somewhat the velocity and amplitude of the upstroke, markedly shortened the plateau, reduced the resting potential, and abolished the contractile force. Strophanthidin, norepinephrine, and calcium given alone each increased the force of contraction. In the presence of tetrodotoxin, strophanthidin sometimes failed to increase the contractile force altogether or produced a rather small and much delayed increase. When, during exposure to tetrodotoxin, norepinephrine or calcium were administered alone, the contractile force increased but only to a fraction of the absolute value reached in Tyrode's solution. However, in each case the increase in force was more than that caused by strophanthidin. In contrast to strophanthidin, which had little effect on the action potential configuration during tetrodotoxin exposure, norepinephrine and calcium increased the plateau toward more positive values. During continuous exposure to tetrodotoxin, norepinephrine or calcium were administered first with the usual small effect. However, if strophanthidin was added, the contractile force increased markedly. The same marked effect was obtained when norepinephrine was added to strophanthidin in the presence of tetrodotoxin. If tetrodotoxin was applied during the positive inotropic effect of either calcium, norepinephrine, or strophanthidin, the force was markedly decreased. Tetrodotoxin shortened the action potential in the low calcium (0.27 mM) solution. The elimination of force in Tyrode's solution suggests that the inward slow current may be decreased by tetrodotoxin. It appears that norepinephrine and calcium (but not strophanthidin) can antagonize the action of tetrodotoxin. (*Supported by Grant HL17451 from the National Heart and Lung Institute, Bethesda, Md.*)

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Abnormal Electrophysiology and Ultrastructure of Atrial Cells in Cats with Spontaneous Cardiomyopathy

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CATS develop hypertrophic and congestive cardiomyopathy similar to the human disease. Myopathy is often accompanied by left atrial dilatation and atrial arrhythmias. We studied the transmembrane potentials of right and left atria isolated from these cats, and found two populations of atrial cells—excitable and inexcitable. Inexcitable cells did not generate action potentials in response to bipolar extracellular stimulation. We studied the electrophysiology and ultrastructure of these inexcitable cells. The mean resting potential of these cells (57.17 ± 0.9 mv.) is significantly lower than the mean resting potential of the excitable cells (69.9 ± 3.6 mv.). Inexcitable cells responded to catecholamines in one of three ways. In some cells catecholamines increased resting potential from 58.8 ± 13.6 mv. to 70.4 ± 6.1 mv., restoring action potentials with fast upstrokes ($\dot{V}_{max}$ = 74.8 V/sec.). In other cells, catecholamines increased resting potential only slightly from 55.1 ± 7.7 mv. to 62.2 ± 7.95 mv., and these cells then generated action potentials with slow upstrokes ($\dot{V}_{max}$ = 1.66 V/sec.). Action potentials with slow upstrokes were sometimes followed by delayed afterdepolarizations. When the drive rate was increased, the amplitude of the delayed afterdepolarizations increased until triggered sustained rhythmic activity occurred. Catecholamines also induced non-triggered automatic activity in cells with slow upstrokes. Slow channel-blocking drugs decreased the amplitude and upstroke of the action potentials with slow upstrokes, abolished the delayed afterdepolarizations, and slowed the catecholamine-induced automatic activity. In a third group of cells, catecholamines increased the membrane potential from 56.2 ± 8.8 mv. to 62.1 ± 8.9 mv., but failed to restore excitability. Ultrastructural studies were done on the atrial tissue obtained from the severely dilated

myopathic cats which showed the greatest percentage of inexcitable cells. We found small cells ($< 5\ \mu$ diameter) that were surrounded by large amounts of fibrous tissue and appeared to lack side-to-side connections, and cells with extensive degenerative changes, such as myofilament loss, aggregated sacroplasmic reticulum, and dilatation of the gap junction portion of the intercalated disc. These changes may cause the loss of excitability and the unusual response to catecholamines. We conclude that abnormal cellular ultrastructure and electrophysiology may cause the atrial arrhythmias that often accompany cardiomyopathy. (*Supported by a Grant-in-Aid from the New York Heart Association.*)

Additional Clinical Experience with Pulsatile Flow

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A new valveless pulsatile assist device (PAD ®) has been developed which converts roller pump flow into synchronized pulsatile flow. The PAD can also be used as an arterial counterpulsator before and after cardiopulmonary bypass (CPB).

The PAD was employed in 400 adult patients undergoing open heart surgery for coronary artery disease, valvular heart disease, or both. Two hundred and ninety of these patients were NYHA Class III or IV or had ejection fractions of <0.3, and 111 of the 400 had left main coronary lesions. The device functioned as a hemodynamically effective arterial counterpulsator before and after CPB. During CPB, pulse pressures of 40 to 50 mm. Hg were readily obtained. Urinary outputs during CPB were increased on the PAD when compared to a control group (9.18 ± 0.68 cc./min. vs. 3.90 ± 0.35 cc./min.). In addition, during CPB, coronary graft blood flow increased an average of $21.4 \pm 6.1\%$ with the PAD. Free plasma hemoglobins after CPB were not elevated. There were two intra-operative and six late deaths (2.0%). Only eight patients (2.0%) had a perioperative myocardial infarction; three of these required intra-aortic balloon pumping and two of these survived.

The PAD is a simple and reliable device for both intraoperative counterpulsation and for creation of pulsatile CPB. More significantly, use of the PAD has decreased both the incidence of perioperative myocardial infarction and the need for postoperative intra-aortic balloon pumping.

(Supported in part by Grant HL 12738-10 from the National Heart and Lung Institute, Bethesda, Md.)

The Effects of N-Acetyl Procainamide on Cardiac Purkinje Fibers

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THE N-acetyl metabolite of procainamide (NAPA), which appears in plasma in significant concentrations in patients receiving procainamide, has been reported to exert antiarrhythmic effects. We examined the effects of NAPA on canine cardiac Purkinje fiber transmembrane potentials. Excised false tendons were superfused with oxygenated Tyrode's solution (Ca^{++} = 2.7 mEq./L, K^{+} = 2.5 or 4.0 mEq./L). Control records were taken after an equilibrium period of at least 60 minutes. The effects of NAPA on the transmembrane potentials were determined after at least 30 minutes of superfusion with Tyrode's solution containing a selected concentration of the drug. NAPA concentrations of 20 and 40 mg./L, which are thought to represent therapeutic and low toxic levels respectively, exerted no significant effect on the rate of phase 4 depolarization, resting membrane potential, action potential amplitude or maximal velocity of the upstroke (phase zero). In contrast, action potential duration (APD) was significantly prolonged by NAPA in a dose-dependent manner. Under given conditions, action potential duration is an inverse linear function of the stimulus frequency. When the regression lines of this relation (APD versus frequency) for Purkinje fibers in drug-free and NAPA containing media were compared, the slopes differed. This kind of modification of the rate dependence of the action potential is consistent with actions of a drug on a time varying dynamic current (e.g., i_{x1}, i_{si}, i_{C1}) rather than on a background current.

In toxic concentrations (i.e., 80 to 240 mg./L) and stimulation rates of six to 40 per minute, NAPA produces a "secondary plateau" at approximately -55 mV during phase 3 of the action potential. This secondary plateau could be suppressed by stimulating the fiber at high frequency, and was accentuated at cycle lengths of 4,000 msec. or longer. At such long cycle lengths, single or multiple spontaneous action potentials were often triggered during the secondary plateau. Secondary plateaus and the triggered action potentials could be abolished by administration of ACh, KCl, or by decreasing the cycle length by accelerating phase 4 depolarization with epinephrine. (*Supported by Grants HL 08508-15 and HL 12738-10 from the National Heart and Lung Institute, Bethesda, Md.*)

Age-Related Changes in Cardiac Cellular Electrophysiologic Properties

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WE determined the age-related changes that occur in canine Purkinje fiber transmembrane potentials. This is important because such changes in the electrical activity of normal cardiac fibers would provide a basis for changes in electrical activity and contraction in the *in situ* heart. In the neonate (0 to 7 days), maximum diastolic potential (MDP) was -83.7 ± 1.2 mV (M ± SE). This increased to -88.3 ± 0.8 mV in mature (66.3 ± 3.6 month) adults and did not change significantly thereafter. Similarly, action potential (AP) amplitude and duration increased ($p < 0.05$) from the neonate to the mature adult and thereafter were unchanged. In contrast, the maximum rate of rise of phase 0 ($\dot{V}_{max}$) which increased from neonates (455 ± 26 V/sec.) to mature adults (552 ± 14 V/sec.) declined significantly in 132.3 ± 4.3 month animals (453 ± 16 V/sec.). Comparing mature adults to old animals, the latter showed significantly greater phase 1 repolarization and significantly lower plateau heights. Purkinje fibers from adult and old dogs then were superfused with graded concentrations of AHR-2666 (a Ca^{++} blocker) or tetrodotoxin (TTX). The effects of TTX on the AP were equivalent for adult and old animals, suggesting that there are not significant age-related changes in the rapid inward current. However, with AHR-2666, significantly greater changes in the magnitude of phase 1 repolarization and the plateau occurred in the older animals. Slow response action potentials were produced in Purkinje fibers from other adult and old animals by replacing superfusate Na^+ with TEA^+. Here, AP amplitude and $\dot{V}_{max}$ were lower ($p < 0.05$) in the old animals. The Ca^{++} blocker verapamil induced a significantly greater depression of the Purkinje fiber action potential in the old than the adult dogs. We conclude that the major age-related change in the transmembrane potential comparing the neonate to the adult is in MDP, and AP amplitude and $\dot{V}_{max}$ changes are probably secondary to these; and that the major change

comparing adult to old animals is in the AP plateau. Pharmacological experiments in fibers with fast and slow response AP suggest that age-related differences in the plateau largely result from changes in the slow inward current carried by Ca^{++} rather than from changes in the Na^{+} current. (*Supported in part by USPHS-NHLBI Grant HL-12738 from the National Heart and Lung Institute, Bethesda, Md., and a grant from the New York Heart Association.*)

Pindolol (LB-46) Therapy for Supraventricular Arrhythmias: A Viable Alternative to Propranolol

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BETA blocking drugs are effective in the treatment of patients with supraventricular arrhythmias. Because propranolol can aggravate bronchospasm and congestive heart failure, beta blocking agents lacking these properties may provide useful alternatives. Pindolol (LB-46) is a beta blocking agent with bronchial sparing properties, no membrane depressive effect, and no direct negative ionotropism. Thirty-one patients with acute supraventricular arrhythmia (paroxysmal atrial tachycardia, rapid atrial fibrillation, rapid atrial flutter) were treated first with a placebo followed by LB-46 in either oral or intravenous form. All patients had been successfully treated with propranolol in the past for their arrhythmia, but 18 patients could not tolerate the drug because of bronchospasm. Underlying diagnoses included idiopathic hypertrophic subaortic stenosis, hyperthyroidism, chronic obstructive lung disease, coronary artery disease, and cardiomyopathy. Following a no-response placebo period, LB-46 converted 12 of 14 patients with paroxysmal atrial tachycardia to normal sinus rhythm without deterioration in pulmonary function parameters or left ventricular function determined from echocardiograms. In 13 patients with atrial fibrillation, 10 demonstrated ventricular rate slowing and two converted to normal sinus rhythm. In four patients with atrial flutter, three patients slowed their ventricular response and one patient converted to normal sinus rhythm. Long-term oral LB-46 therapy sustained these responses (Serial Holter ECG) without changes in pulmonary function or left ventricular function. LB-46 was tolerated in most patients who had propranolol-induced bronchospasm. All patients treated with long-term oral placebos showed a rapid return to the dysrhythmic state. LB-46 appears to be a safe and effective alternative to propranolol in patients with supraventricular arrhythmia, especially if complicated by bronchospasm. The lack of depression in left ventricular function also suggests its use in supraventricular arrhythmias associated with congestive heart failure.

(*Supported by a grant from Sandoz Laboratories*)

Detection of Intermittent Pacemaker Malfunction by Ambulatory Monitoring

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We describe a modification of the standard Holter monitoring technique, which allows rapid reliable recognition of intermittent pacemaker malfunction as well as assessment of the proportional frequency of paced beats. The system utilizes two additional modules interposed between elements of an existing Avionics dual channel system but requires no significant modification to the existing apparatus.

The first module is a 12 cm. x 6 cm. x 3 cm. battery-operated square-wave amplifier worn on the patient's belt and connected between the Channel 2 electrodes and the Channel 2 inputs of the recorder cable. This module detects the occurrence of a pacemaker spike and delivers a square-wave of sufficient width (10 msec.) and amplitude (5 mv.) to be clearly recorded. Channel 1 of the 445 recorder is connected directly to the patient in the usual fashion and records EKG information. The recorded tape, therefore, portrays EKG with or without pacemaker information on Channel 1 and a straight line interrupted by a square-wave impulse with each pacing spike on Channel 2. The second module is a small committed digital computer connected to the Avionics 660 scanner auxilary output jacks. During rapid playback it monitors the temporal relation between pacemaker spike (Channel 1) and QRS complex (Channel 2) and performs the following functions: Detection of pacemaker sensing failure, detection of pacemaker capture failure, detection of complete output failure (pauses), counts paced beats, and counts fusion beats.

Detection of a pacemaker malfunction event returns the scanner to real-time playback and initiates a paper write-out.

Twelve months experience with this fully automated system has allowed detection and documentation of intermittent malfunction of pacemaker units not recognized by conventional methods. We advocate this system for all recently implanted permanent pacemakers before discharge from hospital, routinely each year and for any unexpected palpitations or syncope in a paced patient.

A Drug Interaction Between Digoxin and Quinidine

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To evaluate a possible drug interaction between digoxin and quinidine, we reviewed charts of 863 consecutive cardiology patients seen in a one-year period. Ninety-two of 863 patients received both digoxin and quinidine; 38 were ineligible for further study because of insufficient data and 27 were excluded from analysis because of changing renal function, concomitant therapy with other antiarrhythmic drugs, or both. In 25 of the remaining 27 patients, serum digoxin concentration increased significantly during quinidine therapy: mean concentration was 1.4 ng./ml. before quinidine (range 0.6-3.0) and 3.2 ng./ml. during quinidine (range 1.2-6.4). Anorexia, nausea, and vomiting developed in 61% during combined therapy, and disappeared in 10 of 10 patients in whom digoxin alone was reduced in dose. Three of 13 patients developed new ventricular arrhythmias after starting quinidine; one of these developed ventricular tachycardia and another died suddenly within five days of starting quinidine. *In vitro* studies failed to demonstrate significant alteration in the radio-immunoassay of digoxin by the addition of quinidine.

A prospective study in six patients demonstrated elevations in serum digoxin in each after beginning quinidine. After starting quinidine, serum digoxin increased by 64% ± 13% at 24 hours and by 109% ± 42% at 48 hours even though the digoxin dose was reduced or held constant. Follow-up as long as three months has shown that this increase has been sustained.

We found that serum digoxin continued to rise after beginning quinidine even when digoxin was entirely withheld. This finding makes it unlikely that quinidine causes an increase in digoxin absorption, a decrease in digoxin excretion or a decrease in the metabolism of digoxin. Displacement of digoxin from tissue-binding sites is the most likely explanation for

the acute rise in serum digoxin concentration when quinidine is begun in digitalized patients.

We conclude that quinidine will increase serum digoxin in most patients receiving digoxin, and that this increase may produce adverse gastrointestinal symptoms, ventricular arrhythmias, or both, which may reflect digoxin rather than quinidine toxicity. *(Supported in part by Grants HL-12738, HL-70204, HL-05864, and HL-10608 from the National Heart and Lung Institute and Grant RR-00645 from the Division of Research Resources, Bethesda, Md., and by Grants-in-Aid from the New York Heart Association, the Chernow Foundation, and the Winthrop Foundation.)*

Histamine-Induced Idioventricular Tachyarrhythmias and Their Potentiation in the Thyrotoxic Heart

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We previously demonstrated that the arrhythmogenic effects of histamine are potentiated by hyperthyroidism. In particular, ventricular tachyarrhythmias occur more frequently and last longer. Our present study investigated the electrical mechanisms involved in the generation of histamine-induced ventricular tachyarrhythmias in the thyrotoxic heart, using as a model the isolated guinea pig heart with a permanent atrioventricular conduction block. In this preparation idioventricular rhythmicity is independent of atrial pacemakers.

Guinea pigs were injected with l-thyroxine (i.p., 100 μg./animal/day) for eight days. The induction of the thyrotoxic state was characterized by weight loss (−29%) and sinus tachycardia (+50%). The animals were killed, and their hearts were excised and mounted in a Langendorff apparatus. Following an equilibration period, the right atrium was cut open and a ligature was placed around the area of the bundle of His. This resulted in permanent atrioventricular dissociation. A bipolar surface electrogram was continuously recorded. In the hearts from control animals histamine increased the idioventricular rate. Acceleration of the idioventricular rate resulted from an initial gradual enhancement of the firing rate of the original ventricular pacemaker (i.e., increase in automaticity), followed by the sudden appearance of faster ventricular rhythms accompanied by a pacemaker shift (i.e., creation of reentrant circuits, induction of afterdepolarizations, or both). In the hearts from thyrotoxic animals histamine increased the idioventricular rate that did not result from an acceleration of the original pacemaker, but almost exclusively from the creation of new pacemakers. Histamine-induced pacemaker shifts occurred earlier, with greater frequency, and lasted longer.

We suggest that thyrotoxicosis sensitizes the ventricular myocardium to the arrhythmogenic effects of histamine. The increased severity of the arrhythmias probably results from the development of reentrant circuits, afterdepolarizations, or both. (*Supported by USPHS Grant GM20091 from the National Institute of General Medical Sciences and Grant F32HL05536 from the National Heart and Lung Institute, Bethesda, Md.*)

Intracellular Na Ion Activity of Sheep Purkinje Fibers

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FOR intracellular application we prepared Na^+-selective glass microelectrodes by utilizing Thomas's design (*J. Physiol. 210:*82P, 1970) and studied some of their properties. Na^+-selective glass micropipettes with a sealed tip less than 1μ were insulated with a usual glass micropipette so that the Na^+-selective micropipette was recessed in the insulating micropipette. The selectivity of the microelectrodes for Na^+ over K^+ was decreased with aging in 3 M NaCl (filling solution), indicating that the microelectrodes should be used as soon after filling as possible. As the Na^+-selective exposed tip length decreased, response time became faster while the selectivity decreased and the microelectrode resistance increased. Thus, intracellular application required an optimum exposed tip length for high selectivity, low resistance, and fast response time. We made the microelectrodes with an exposed tip length between 30 and 70 μ and a tip-to-tip length less than 10μ. The mean value of Na ion activity in the fibers was 5.8 $\pm$ 1.3 mM (S.D., n = 15). The mean value of Na ion activity in Tyrode solution was 110.9 $\pm$ 1.2 mM (S.D., n = 7). These Na ion activities result in an equilibrium potential of + 74 mV for the Na ion. In the fibers the mean value of resting membrane potential was -80.4 $\pm$ 2.9 mV (S.D., n = 54). (*Supported by USPHS Grant HL 21136 from the National Heart and Lung Institute, Bethesda, Md., and an AHA Established Investigatorship.*)

Altered Bradykinin (BK) Metabolism and the Resultant Circulatory Effects During Acute Hypoxia in Dogs

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We have shown that acute hypoxia decreases angiotensin I conversion in intact dogs, using a blood pressure response bioassay (*Fed. Proc. 36:*630, 1977). Because bradykinin (BK) is also a substrate for converting enzyme, we further characterized this phenomenon by studying instantaneous clearance of BK across the lung using radioimmunoassay. In 43 anesthetized, paralyzed dogs ventilated with room air or hypoxic gas mixtures, BK was infused continuously into the femoral vein and blood was drawn simultaneously from catheters fluoroscopically placed in the right and left atria. The difference in BK levels across the lung (instantaneous clearance) decreased linearly with decreasing PaO_2 ($r = 0.88$, $p < 0.01$) from a clearance of 99.5% at a PaO_2 of 97 Torr to 6.2% at a PaO_2 of 20 Torr. This hypoxic inhibition occurred within two minutes and was rapidly reversible with normoxia. Venous BK levels at which a detectable rise (> 0.11 and < 0.15 ng./ml.) in the arterial circuit first occurs (spillover level) decreased as PaO_2 fell.

To assess the effect of elevated BK in hypoxic dogs, 2.5 μg./kg./min. of BK was infused in eight hypoxic dogs and changes in cardiac output (CO) and systemic vascular resistance (SVR) compared in these dogs and 12 hypoxic controls. Circulating BK rose to 35.5 ng./ml. in the BK-infused dogs; SVR decreased to 68.9% and CO rose to 141.8% of baseline. In the control dogs, SVR increased to 133.6% and CO fell to 86.4% of baseline.

These experiments suggest a circulatory function for bradykinin in hyperkininemic states with hypoxia resulting in an increase in CO and a decrease in SVR. This combination may enhance peripheral blood flow. Because converting enzyme activity in hypoxic tissue is closely related to O_2 tension, local levels of angiotensin II and bradykinin may vary in vascular beds with different O_2 tensions, providing a graded mechanism for blood flow autoregulation. (*Supported by Grants HL 06012, HL 14218 (SCOR) and HL 15832 from the National Heart and Lung Institute, Bethesda, Md.*)

Utility of Single-Dose Thallium-201 Myocardial Perfusion Scanning for the Detection of Coronary Artery Disease

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CONVENTIONAL myocardial perfusion scanning with thallium-201 requires the administration of two doses of tracer, one during exercise and the other at rest. It has been suggested that serial imaging after a single dose of tracer administered during exercise provides equivalent information. The present study evaluates this new single-dose technique.

Thallium-201 myocardial perfusion scans were performed after exercise and four hours later in 128 patients with suspected coronary artery disease (CAD). Coronary arteriography was performed in all patients. Ninety-four of the patients had significant coronary artery lesions (at least 70% luminal narrowing). Scans were interpreted by two experienced observers without knowledge of angiographic or electrocardiographic (ECG) results. Interobserver disagreement was 8%.

In the 34 patients without CAD, two had Q waves on the resting ECG (6%), three had perfusion defects on the four-hour scan (9%), four had ischemic ST-segment depression of at least 0.1 mV on the exercise ECG (12%), and six had a new perfusion defect on the exercise scan (18%).

In the 94 patients with CAD, 42 had Q waves on the resting ECG (45%) while 52 had defects on the four-hour scan (55%). This difference is not statistically significant. Fifty-nine of the CAD patients had an ischemic exercise ECG (63%) while 81 had a new perfusion defect on the exercise scan (86%), a statistically significant difference ($p < 0.01$).

Overall, 88 of the 94 patients with CAD had a perfusion defect on either the four-hour scan or the exercise scan (94%), including 34 of 40 patients with single-vessel disease and all 54 patients with multiple-vessel disease.

Patients with CAD were subdivided on the basis of the resting ECG. In the patients with a normal resting ECG, the prevalence of an ischemic exercise ECG (27 of 35, 77%) was not significantly different from the

prevalence of a new perfusion defect on the exercise scan (29 of 35, 83%). However, of those patients with an abnormal resting ECG, significantly more had a new perfusion defect on the exercise scan (52 of 59, 88%) than had an ischemic exercise ECG (32 of 59, 54%) ($p < 0.01$).

Thus, single-dose thallium-201 myocardial perfusion scanning detects a high proportion of patients with CAD, with less radiation exposure and at a lower cost than the usual double-dose procedure. The major usefulness of the technique is in the evaluation of patients with an abnormal resting ECG. (*Supported by a New York Heart Association Fellowship (*) and by Grants HL-21006 and HL-14148 from the National Heart, Lung and Blood Institute, Bethesda, Md.*)

Rapid Development of Tachyphylaxis to Prazosin Mediated Preload and Afterload Reduction in Refractory Congestive Heart Failure

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INITIAL doses of prazosin (PZ) have been reported to increase markedly (↑) cardiac index (CI) and reduce (↓) left ventricular filling pressure (LVFP) in patients with severe congestive heart failure (CHF), but the effectiveness of repeated doses has not been demonstrated. To do so, we administered three serial doses of 5 mg. of oral PZ (mean 86 μg./kg.) at 12- to 24-hour intervals to each of eight patients with CHF, followed by a 10 mg. dose in five patients. Thermodilution CI (L/min./M^2), mean arterial pressure (MAP, mm. Hg), LVFP, mean right atrial pressure (MRAP, mm. Hg), and systemic vascular resistance (SVR, dynes-sec.-cm.$^{-5}$) were determined every 30 minutes for 12 hours after each dose. The baseline hemodynamic variables before each administration of PZ were similar. Mean changes for eight patients at peak effects on each variable were as follows:

	1st 5 mg.	*2nd 5 mg.*	*3rd 5 mg.*	*10 mg.*
CI	↑ 0.87 ± .08***	↑0.41 ± .11**	↑0.19 ± .11	↑0.39 ± .11*
LVFP	↓10.7 ± 0.8 ***	↓4.7 ± 1.2 **	↓2.0 ± .11	↓4.8 ± 1.0 *
MRAP	↓ 7.5 ± 0.8 ***	↓2.7 ± 0.9 *	↓1.2 ± 0.9	↓3.0 ± 0.5 **
MAP	↓18.9 ± 2.6 ***	↓6.6 ± 1.7 **	↓2.6 ± 1.8	↓6.0 ± 0.7 **
SVR	↓964 ± 146 ***	↓446 ± 122 **	↓230 ± 117	↓394 ± 92 *

***=$p < .001$, **= $p < .01$, and *= $p < .05$

Whereas marked hemodynamic improvement was observed with the initial 5 mg. dose of PZ, repeated administration produced effects of progressively less magnitude such that with the 3rd 5 mg. dose, no significant hemodynamic changes were observed. Diuresis with high doses of furosemide failed to restore PZ responsiveness, and even 10 mg. doses had only small overall effects. Six of the eight patients demonstrated no significant hemodynamic or clinical improvement at any dose level of PZ (up to 45 mg. daily) after the first two doses. Only two patients had persistent vasodilator effects sufficient to justify chronic ambulatory therapy. In conclusion, previous reports of the beneficial hemodynamic effects of PZ in patients with CHF largely represent a "first dose phenomenon" which is not sustained with repeated administration of the drug by either hemodynamic or clinical evaluation. (*Supported by a grant from the Heart Research Foundation, Inc.*)

Use of Phentolamine in Chronic Congestive Heart Failure

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PHENTOLAMINE can improve patients in congestive heart failure due to its inotropic effect and its vasodilating action. Use of phentolamine given orally has not been adequately investigated in patients with chronic heart failure. Therefore, eight outpatients in chronic heart failure due to underlying coronary artery disease or valvular disease received 50 mg. of phentolamine four times a day for two weeks. All of the patients received digitalis and diuretics throughout the study. Echocardiograms and phonocardiograms were obtained prior to phentolamine treatment and two weeks after its introduction. The results were as follows:

	Control	*Phentolamine*	*P Value*
Pulse Rate	87	86	N.S.
LVET	439	451	N.S.
Q-S2 Index	595	588	N.S.
Pre-ejection period	157	137	<0.001
PEP/LVET	0.48	0.40	<0.01
Ejection fraction	54	63	<0.01
%change in minor axis	29	36	<0.01
Velocity circumferential fiber shortening	1.09	1.26	<0.05
Left atrial dimension	5.3	4.6	<0.05

Phentolamine improves cardiac hemodynamics in chronic heart failure patients.

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Usefulness of Carotid Sinus Pressure in Detecting the Sick Sinus Syndrome

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ELECTROPHYSIOLOGICAL studies are often normal in the sick sinus syndrome (SSS). His bundle electrograms (HBE) with right atrial pacing and sinus node recovery times (SNRT) were obtained from 30 patients with the SSS and 20 patients without the the SSS. Carotid sinus pressure was also applied to all patients during the HBE studies. Corrected SNRT, the observed SNRT minus the unpaced cycle length, was calculated, as was the corrected carotid sinus recovery time, the observed carotid sinus recovery time (SNRT) minus the unpaced cycle length. In the 30 patients with the SSS, the SNRT was greater than 1,680 msec. in the five patients, with a sensitivity of 17%. The CSRT was greater than 2,000 msec. in 16 patients, with a sensitivity of 53%. The corrected SNRT was greater than 450 msec. in eight patients, with a sensitivity of 27%. The corrected CSRT was greater than 450 msec. in 22 patients, with a sensitivity of 73%. Thus, the corrected CSRT is a major provocative test for the SSS. In the 20 patients without the SSS, the SNRT and CSRT were normal in every patient with a specificity of 100%. The corrected SNRT was less than 450 msec. in every patient while the corrected CSRT was less than 450 msec. in 19 of 20 patients. The average SNRT was 997 msec. while the average CSRT was 1,054 msec. ($r = 0.71$, $p < 0.001$). Therefore, the carotid sinus recovery time is a noninvasive estimate of the sinus node recovery time in patients without the SSS.

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Biosynthetic Events in the Regulation by Aldosterone of Sodium Balance

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We studied the cellular events in aldosterone's (Aldo) enhancement of sodium transport, using the toad urinary bladder as a model for the kidney distal tubule. To characterize the hormone-induced modifications of the cell-plasma membranes, we devised a method to isolate this tissue fraction so that hormone-induced proteins could be identified and analyzed. Mucosal cells were disrupted by nitrogen cavitation, and plasma membrane vesicles were prepared by density gradient centrifugation. These membranes, identified by electron microscopy, were characterized by an 11-fold enrichment in 5'-nucleotidase and a large decrease in activity of contaminating marker enzymes. This technique was used to prepare membranes of cells from bladders incubated in ^{3}H-labelled amino acids plus Aldo and ^{14}C-labelled amino acids plus Aldo and cycloheximide. These plasma membranes were dissolved and analyzed by SDS-urea polyacrylamide gel electrophoresis (PAGE) for alterations in the isotope ratio indicative of protein synthesis. The membranes prepared from the mitochondria-rich (MR) cells showed three proteins with elevated isotope ratios (mol. wts. 170,000, 85,000, and 12,000) indicating specific hormone-induced synthesis, while no plasma membrane proteins from the granular (G) cells showed similar peaks. mRNA isolated from MR cells was used to synthesize protein in a rabbit reticulocyte (cell-free) system; in this system new protein synthesis is wholly dependent upon the addition of exogenous mRNA. After incubation for 90 minutes the protein was precipitated and analyzed by PAGE. Our data suggest that the proteins synthesized *in vitro* are similar to the Aldo-induced proteins synthesized *in vivo*. Thus we believe we have progressed in the elucidation of some of the final effector steps in the renin-angiotensin-aldosterone axis. (*Supported by the American Heart Association and the New York Health Research Council.*)

*Molly Berns Senior Investigator of the New York Heart Association.

Left Ventricular Mechanics of Myocardial Assist Devices:Counterpulsation Compared to Left Atrial-Aortic Bypass in Dogs

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COUNTERPULSATION (CP) and left atrial-aortic bypass (LABP) have both been used successfully to salvage patients with depressed myocardial function following cardiac surgery, yet the specific effects of each technique on the physiology of left ventricular (LV) muscle contraction have not been defined. Accordingly, a changing volume spherical LV model was utilized to calculate peak LV systolic wall stress (STR) and pressure-volume stoke work (PVW) in 10 anesthetized, open chest dogs during maximum achievable CP (combined intraaortic balloon and direct aortic root blood pumping), LABP (partial bypass of 62 ± 8% total cardiac output in six, total bypass in four), and control (C) states. The data base analyzed by computer for the calculations included high fidelity LV pressure and dP/dt by micromanometer, instantaneous aortic root flow by electromagnetic flowmeter, and end diastolic volume extrapolated from LV end diastolic pressure using postmortem LV pressure-volume curves.

PVW during CP (23 ± 5 (S.E.) gm.-m.) was essentially unchanged from C (26 ± 6 gm.-m.) yet significantly decreased with partial LABP to 8 ± 2 gm.-m. ($P < 0.02$ versus C and CP). Total LABP reduced PVW to 0 gm.-m. STR was reduced from 94 ± 2 gm./cm.^{2} during C to 80 ± 10 gm./7cm.^{2} ($p < 0.05$) with CP. Partial LABP decreased STR to 72 ± 8 gm./cm.^{2} ($p < 0.003$ versus C) yet this effect was not significantly different from that of CP. Total LABP reduced STR to 36 ± 9 gm./cm.^{2} ($p < 0.003$ versus C, $p < 0.03$ versus CP).

Partial and total LABP reduce the external work of the LV myocardium on the circulating blood volume while CP has no such effect. However, because STR correlates highly with myocardial oxygen consumption, we conclude that partial LABP, unlike total bypass, may have little advantage over CP in myocardial oxygen conservation. (*Supported in part by PHS Grant No. HL12738-10 from the National Heart and Lung Institute, Bethesda, Md.*)

Function of Hearts Conditioned by Running and by Swimming

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FEW data are available comparing the two popular modes used to condition rats physically, i.e., swimming and treadmill running, and none have compared their effects on heart function. Therefore, performance of hearts from male rats conditioned by swimming (S) or running (R) for 8 to 10 weeks at similar intensities and durations were compared with sedentary controls (C) in an isolated working heart apparatus. Hearts were analyzed at similar heart rates over a range of 5 to 20 cm. H_2O atrial filling pressure (AP). End-diastolic volume (EDV) was determined using a dye-dilution technique, and instantaneous ventricular volumes during ejection were determined by subtracting integrated aortic flow from EDV.

Resting heart rates and body weights were less in S and R than in C ($p < 0.05$), indicating that training effects had been achieved in both conditioning groups. Enhanced pump and muscle function was observed in both groups of conditioned hearts, particularly at higher AP. Values at 20 cm. H_2O AP were (results are the means of 10 hearts; * = $p < 0.05$ versus C):

	C	*S*	*R*
EDV (ml./g.)	3.32	3.18	3.31
EF	0.41	0.50*	0.49*
CO (ml./g.)	460	539 *	543 *
MP (10^6 ergs/g. sec.)	3.28	4.35*	4.03*
Neg dP/dt (mm.Hg/sec.)	2530	3084*	2773
Vcf (cm./sec.)	8.4	11.0 *	10.9 *

g = gram dry LV wt; EF = ejection fraction; CO = cardiac output; MP = max power; Neg dP/dt = maximum rate of fall of LV pressure; Vcf = velocity of circumferential fiber shortening

Actomyosin ATPase activity was significantly elevated in S (0.663 μM Pi/min./mg. protein) in comparison to R (0.551) and C (0.535) ($p < 0.001$).

Because atrial and aortic pressures were the same in all groups and EDV were also similar, an increased EF is evidence of enhanced contractile performance in S and R. This was confirmed by other contractility indices. Increases in both rates or relaxation and in actomyosin ATPase activities in S but not R versus C suggest differences in biochemical adaptations between swimming and running. (*Supported by USPHS Research Grant HL 15498 and Institutional Research Service Award HL 07071 from the National Heart and Lung Institute, Bethesda, Md.*)

Structure and Function of Canine Cardiac Myosin During Pressure-Overload Cardiac Hypertrophy

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STUDIES were conducted of myosin from the left and right ventricles of normal canine hearts and hypertrophic canine hearts at five weeks and 13 weeks after aortic banding. On SDS-polyacrylamide gel electrophoresis, cardiac myosin shows degraded heavy chains (70,000-180,000 mol. wt.), the proportion of which is greater in myosin from hypertrophic hearts than normal hearts. Interestingly, comparable degradation occurs in preparations from left and right ventricles of banded hearts, although only the left ventricle was subjected to hemodynamic stress. Heavy chain fragmentation in the presence of dodecyl sulfate appears to have a complex origin, involving a nonenzymatic stochastic process and proteolysis due to contaminant proteases. In addition, the susceptibility of heavy chains to protease-dependent proteolysis differs in myosin from normal and hypertrophic hearts. With precautions to minimize proteolytic artifacts, myosin preparations from left and right ventricles of normal and hypertrophic hearts exhibit comparable subunit composition, with molar ratios of heavy chains (200,000 d.), light chain L1 (27,000 d.), and light chain L2 (18,000 d.). In studies of the microheterogeneity of myosin light chains, charge electrophoresis and a newly developed two-dimensional SDS-isoelectric focusing method reveal the same subunits in preparations from normal and hypertrophic hearts.

There is also evidence that ATPase activity is altered in purified myosin from hypertrophic hearts. At five weeks after aortic banding there is diminished K^+/EDTA-ATPase and no significant change in Ca^{++}-ATPase in myosin from hypertrophic hearts as compared with normal hearts. Similar activities are obtained for left and right ventricle myosin. A wide variation of K^+/EDTA-ATPase among individual preparations of myosin may be related to the extent of cardiac hypertrophy, in that activity is normal or slightly diminished in mild hypertrophy and diminished approximately 50% in moderate hypertrophy. Insofar as there is no evidence for

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different myosin isozymes in normal and hypertrophic canine hearts, the observed changes in myosin ATPase during pressure-overload cardiac hypertrophy may reflect denaturation or other modification of myosin *in vivo*. *(Supported in part by Grant AM-06165 from the National Institute of Arthritis, Metabolism, and Digestive Diseases and Grant HL/AM-16596 from the National Heart and Lung Institute, Bethesda, Md., the New York Heart Association, and the New York State Health Research Council.)*

The Effect of Exercise Training on the Ventricular Response to Exercise: An Echocardiographic Analysis

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THE roles of the Frank-Starling mechanism and enhanced ventricular contractility in effecting the increased stroke volume associated with exercise training remains subject to debate. Echocardiography provides a method for the reliable measurement of left ventricular internal dimensions (end-diastolic, EDD, and end systolic, ESD) at rest and during supine exercise. Fourteen healthy, sedentary students were studied by echocardiography at rest and during the last 30 seconds of supine ergometric exercise (300 KPM/min.) before and after 14 weeks of intensive exercise training. Maximum oxygen consumptions ($\dot{V}O_{2max}$) were measured during a graded ergometric exercise protocol before and after training.

Echocardiographic measurements of end diastolic dimensions (EDD), end systolic dimensions (ESD) and calculation of stroke dimension (SD = EDD-ESD) and fractional dimension shortening (SD/EDD) were made, as

were resting end-exercise heart rates and blood pressure before and after training. A control (nontrained) group of 11 healthy subjects were evaluated in an identical manner before (BT) and after (AT) a 14-week interval.

The trained group showed a significant mean increase in $\dot{V}O_{2max}$ (31.1%) and a decrease in resting and end-exercise heart rates (9% and 11% respectively). Echocardiographic measurements and calculations in the experimental group are summarized below.

	Before training		*After training*	
	Rest	*End-exercise*	*Rest*	*End-exercise*
EDD, cm.	4.7 ± 0.4	4.6 ± 0.4	5.0 ± 0.4′	5.0 ± 0.4
ESD	3.2 ± 0.4	2.1 ± 0.4′	3.2 ± 0.4	3.0 ± 0.3′′
SD	1.4 ± 0.2	1.7 ± 0.2′	1.7 ± 0.2′	2.0 ± 0.2′′
SD/EDD	0.32 ± 0.03	0.37 ± 0.03′	0.35 ± 0.03′	0.41 ± 0.03′′

′$P < 0.05$ compared to rest BT or ′′end-exercise BT

Control group values did not differ significantly from the experimental group before training and did not change over the control period.

Training is associated with an increase in resting EDD and no change in ESD. The resting SD is increased as is the SD/EDD. During exercise EDD remained unchanged and ESD fell. The increase in SD was associated with an increase in SD/EDD. This response to exercise was noted both BT and AT, the AT exercise changes occurring from the elevated resting EDD, SD, and SD/EDD.

During supine exercise the increase in stroke volume in the intact heart is mediated by an enhanced contractile state, whereas the training response (increased resting and exercise stroke volumes consequent to training) is mediated by both an enhanced contractile state and the Frank-Starling mechanism.

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Regional Effects of Lidocaine in Patients with Coronary Artery Disease

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STUDIES of isolated tissues and canine models of myocardial ischemia have demonstrated that lidocaine slows conduction in abnormal but not in normal tissues. To determine lidocaine's effects on conduction in patients with coronary artery disease, we studied seven patients following left anterior descending coronary artery (LAD) bypass graft surgery. In these patients, bipolar electrodes were placed in the atrium, right ventricle (RV), and left ventricle in the distribution of the LAD (LV). At a constant atrial paced rate, conduction intervals were measured from the earliest onset of the QRS in three simultaneously recorded surface ECG leads to the major deflection of the electrograms recorded in LV and RV. On postoperative day seven, lidocaine was administered as a 100 mg. bolus followed by a 4 mg./kg. infusion for two hours. At peak effect, with a mean lidocaine level of 2.5 ± 0.5 mg./ml., lidocaine slowed conduction in the LV by a mean of 6 ± 1 msec. (14 ± 2%) ($p < 0.001$) and in the RV by 1 ± 0.3 msec. (4 ± 1%) ($p < 0.01$). QRS duration changed 1 ± msec. (4 ± 1%) (NS). The changes returned to baseline by two hours after discontinuation of the infusion. The difference in lidocaine's effect between LV and RV was significant ($p < 0.001$, Student's t-test).

We conclude that, in patients with coronary artery disease, lidocaine has local anesthetic effects in slowing conduction; the effects of lidocaine vary with the region of ventricular myocardium studied; and that lidocaine slows conduction more in the LV than RV. This difference may be due to potentiation of drug effect in left ventricular tissue that is abnormal due to the effects of chronic coronary artery disease. (*Supported by NIH Grant 18801 and a Grant-in-Aid from the New York Heart Association.*)